REMARKS

Reconsideration of this application is respectfully requested.

Claims 284-372 are pending in this application. Claims 284, 337 and 348 have been amended hereinabove. No other claims have been amended, added or canceled. Accordingly, claims 284-372 as amended are presented for further examination on the merits.

A minor informality (double dashes in a chemical name) has been corrected on page 59, line 15.

In a sincere effort to define their invention more clearly, Applicants have amended each of claims 284, 337 and 348. In claim 284, the second and last step of the detection process has been amended to read "(b) detecting the presence of said detectable Sig moieties in any of the oligo- or polynucleotides which have hybridized to said nucleic acid of interest." In claim 337, the offensive designations "(i)" and "(b)" at the beginning of line 4 and also the third line from the end of the claim, respectively, have been deleted. Finally, in claim 348, the extraneous line in the last line of the incorporation step (B) has also been deleted. The deleted line in claim 348 read "(b) said oligo- or polynucleotide of interest;". It is believed that none of the foregoing amendments to the claims constitutes the insertion of new matter. Instead, these amendments have been effected to meet the Examiner's requirements or to adopt his suggestions for claim clarity. Entry of these amendments is respectfully urged.

Before turning to the substantive issues in this case, Applicants acknowledge, with appreciation, the indication on page 2 in the latest Office Action that certain rejection and/or objections have not been reiterated from previous office actions, and have been deemed withdrawn.

Applicants also acknowledge the Examiner's suggestion on page 2 of the latest Office Action for a claim of priority under 35 U.S.C. §120. Applicants would like to point out that amendments were made to the specification for the purpose of claiming §120 priority. These amendments

were effected in Applicants' September 28, 1995 Preliminary Amendment. See, in particular, pages 2 and 3 of that Preliminary Amendment.

In addition, Applicants wish to avail themselves of the provisions of 37 C.F.R. §129(a) by filing concurrently herewith a request to withdraw the finality of the January 6, 1998 Office Action. The Examiner was kind enough to note on pages 13 and 14 of the Office Action that this application qualifies for such treatment.

The Objection and Rejection Under 35 U.S.C. §112, First Paragraph

Claims 284-373 stand rejected for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. In the January 6, 1998 Office Action (pages 3-5), the Examiner stated:

> Consideration of the disclosure as filed has failed to reveal support for newly submitted claims 339-341. It is noted that claims 79-82 and 90 disclosure some specific linkage groups but none of the same scope as newly submitted claims 339-341. The linkages of claims 339-341, 350, 351, 353, 354, 356-358 therefore are NEW MATTER. This rejection is necessitated by amendment.
>
> The optional template dependent or independent limitations of claims 346 and 363 have not been found as filed and are therefore NEW MATTER. This rejection is necessitated by amendment.
>
> The specific localization of modified nucleotides as given in instant claims 365-367 has also not been found as filed and is therefore NEW MATTER. This rejection is necessitated by amendment.
>
> The electrophoretic separating as given in instant claim 368 has also not been found as filed and is therefore NEW MATTER. This rejection is necessitated by amendment.
>
> Consideration of the disclosure as filed has also failed to reveal written description of sequencing gel practice as now given in instant claims 329 and 348 etc. This practice therefore is NEW MATTER. This rejection is necessitated by amendment.
>
> The following rejection is reiterated from the office action, mailed 12/28/95. Applicants argue that the content of two previous patents should overcome this rejection. In response, the rejection is based on a lack of written description "as filed" in the instant application. The content of other disclosures is moot and non-persuasive in overcoming the rejection because such other disclosures do not support what instant written basis existed as filed. There

> other disclosures therefore are not directed to the basis of this rejection which is a lack of support for the below summarized limitations "as originally filed". This rejection is repeated as follows and additionally applied to newly added claims that also contain the NEW MATTER limitations as necessitated by amendment. The limitations directed to the covalent attachment of a Sig moiety to a nucleotide base limited to positions other than C^5 of pyrimidines, C^8 of purines, or C^7 of deazapurines as presently given in claim 284 is NEW MATTER. No such negative limitations which are inclusive of numerous other base modification locations are cited in the specification. The presently pending claims dependent from claim 284 also contain the NEW MATTER due to their direct or indirect dependence from claim 284. It is noted that none of these dependent claims are limited so as to not contain said NEW MATTER limitation. Even claims such as 310 contain this limitation in that its Sig attachment limitation only limits the nucleotide (iii) selection but that the claim lacks wording such that this (iii) selection is the only labeled nucleotide type.

The rejection for new matter is respectfully traversed.

With respect to the specific linkage groups, it is believed that these embodiments as set forth in claims 339-341, 350-351, 353-354 and 356-358 are fully supported by the specification as originally filed. For example, the language that the linkage group contains an amine (claim 339) or a primary amine (claim 340) is supported by the specification at page 11, last paragraph; and page 18, third paragraph.

Regarding the matter of template dependent or independent limitations (claims 346 and 363), electrophoretic separation (claim 368) and sequencing gel practice (claims 329, 348, etc.), Applicants respectfully contend that all such embodiments would have been reasonably conveyed to the skilled artisan by virtue of their disclosure on page 84, second paragraph. There, Applicants disclose:

> This type of self-signaling molecule can be used to monitor any nucleic acid hybridization reaction. It is particularly important for detecting nucleic acids in gels (for example, sequencing gels).

Any person skilled in the biotechnology arts and in nucleic acid technology in particular would readily appreciate the implications of the above-quoted statement. In this regard, Applicants would like to bring to the Examiner's attention two definitions for sequencing gel.

The first by Oliver and Ward appears in A Dictionary of Genetic Engineering [Cambridge University Press, Cambridge, 1985, page 100] and it defines "sequencing gel" as:

> A long polyacrylamide slab gel which has sufficient resolving power to separate single-stranded fragments of DNA or RNA which differ in length by only a single nucleotide. Electrophoresis is carried out at high voltage and with the gel in a vertical position. Urea is usually included in the gel mixture as a denaturing agent. This prevents internal base pairing within the single-stranded molecules and ensures that their relative speed of migration is solely dependent on their length. Such gels are used to separate the radioactively labeled products of, for example, the Maxam-Gilbert or the Sanger sequencing reactions.

A second definition of "sequencing gel" comes by way of Stenesh' Dictionary of Biochemistry and Molecular Biology [Second Edition, John Wiley & Sons, New York, 1989, page 437]. There, a sequencing gel is defined as:

> A long, thin polyacrylamide gel slab used for nucleic acid sequencing.

A copy of Ward and Oliver's and Stenesh' definitions are attached to this Amendment as Exhibits 1 and 2, respectively.

In view of the foregoing remarks and submitted exhibits, Applicants respectfully request reconsideration and withdrawal of the new matter rejection.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 284-372 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to a scope of covalent attachment sites of the cited "Sig" moiety to bases of nucleic acids wherein said sites are either the N^2 of guanine, the N^6 of cytosine, or the C^6 of uracil. In the Office Action (pages 5-8), the Examiner stated:

> A thorough review of the disclosure as filed has revealed that the chemistry by which nucleic acid bases may be modified so as to attach a "Sig" moiety only is disclosed for the above four attachment sites within the scope of claims 284 etc. For example, the instant disclosure does not discuss in any way the preparation of N-1 or N-3 modified purines or N-3 or C-2 modified pyrimidines. It is noted that

claims 284 etc. are already limited in that certain other, non-base, attachment sites on purines, pyrimidines, and deazapurines are not within the scope of the claims for the at least one modified base in probes used in the claimed methods. It is also noted that certain generalized labeling methods are instantly disclosed such as the formaldehyde coupling of cytochrome C as a bridge between biotin and a nucleic acid molecule on page 58 but that such generalized labeling of a nucleic acid probe lacks both instant disclosure as well as predictability as to where the attachment site is on the probe and therefore fails to predictably form attachments as instantly claimed and thus is deemed to fail to enable the broad scope of specific base modifications of the instant claims. Ruth is herein cited as summarizing the lack of knowledge at the time of the instant filing regarding the preparation of nucleic acid hybridization probes which contain a signalling moiety. The earliest disclosure of said summary of Ruth is 2/22/83 which is the filing date of the earliest patent thereof and which is also less than a year after the filing date of the instant application. This therefore summarizes the lack of broad hybridization probe preparatory knowledge even after the instant filing date. Ruth summarizes the preparatory knowledge for signal moiety containing labeled probes in column 1, line 43, through column 3, line 45. As cited therein nucleic acid hybridization probes may be prepared either chemically or enzymatically. Enzymatic synthesis using nick translation is discussed wherein certain base modifications have been incorporated into probes but limited in use due to several factors. One of these factors is that only certain modifications may be incorporated by enzymes. Ward et al. (P/N 4,711,955) summarize the factors that were viewed as limitations on modified nucleotides in column 6, line 36, through column 7, line 17, and thereinafter discuss specific base modifications with detailed and lengthy chemical steps. Ruth at column 3, lines 26-45, also summarizes that chemical synthesis has not been disclosed in the prior art as incorporating modified or reporter group containing nucleotides. Further consideration of Ruth reveals that specific base modifications are therein disclosed such as at column 10, line 57, through column 20 which are accomplished via a lengthy series of detailed reactions including the masking and unmasking of reactive side groups to prevent unwanted modifications. Ruth and Ward et al. are deemed representative of those skilled in the art at about the time of the instant filing date of the instant disclosure. In summary, those skilled in the art at the time of filing of the instant invention viewed the preparation of signal moiety containing nucleic acid probes as lengthy and detailed procedures that were discussed as being accomplished only for certain specific base modifications. It is noted that Ruth or Ward et al. only disclose base modifications at the following sites: C-8 of purines and the C-5 of pyrimidines, N^6 of adenosine, and N^2 of guanosine, and N^4 of cytosine, and C-7 of 7-deazapurines. This documents the lack of enablement of most specific base modifications without detailing lengthy preparatory procedures for those skilled in the art at the time of the instant filing date. Therefore it is deemed undue experimentation to prepare base modified nucleic acid hybridization probes wherein the site of base modifications is other than N^2 of guanine, the N^6 of adenine, the N^4 of cytosine, or the C-6

of uracil within the scope of instant claims 240 etc. It is again noted that the instant claims are limited so that base modifications at the C-8 of purines, the C-5 of pyrimidines, and the C-7 of 7-deazapurines are not within their scope. This rejection is reiterated and newly applied as necessitated by amendment due to newly added claims. The rejection has not been argued on its merits other than pointing to issued patents.

Claims 284-372 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to "SM" moieties which are either ribose or deoxyribose. It is noted that claim 284, lines 13-15, cite "PM" attachment points when the nucleotide compound is either a deoxyribonucleic or ribonucleotide but does not therein limit the "SM" moiety to a sugar moiety that is present in either of these nucleotide types. Thus, the scope of "SM" is only presently limited in claims 284 etc. to being a "sugar moiety" which is much broader in scope than that of ribose or deoxyribose. It is noted that there is no instant discussion as to how to practice the synthesis of nucleotides with "SM" moieties other than that of ribose or deoxyribose. For example, how does someone wishing to utilize glucose as "SM" practice the instant claims? It is noted that in order to broadly practice sugar moieties usage both the synthesis of "PM" attachment is required as well s the "Sig" attachment. Additionally hybridization between the nucleic acid of interest and the oligo- or polynucleotide must still be permitted. No guidance whatsoever has been instantly set forth directed to accomplishing this broad sugar moiety practice other than that directed to ribose or deoxyribose sugars. It is noted additionally that the numerous examples given in the specification do not include any sugar practice other than ribose or deoxyribose. In the above scope rejection directed to base labeling practice the need for detailed and lengthy procedures to enable the person skilled in the art to prepare nucleotide analogs as well as their incorporation into polymers is summarized. These disclosures include complex chemical protection requirements including those directed to sugar side group protection as well as considerations such as whether enzymes would recognize and incorporate nucleotides into polymers or not as well as other considerations as discussed above. Thus, it is deemed undue experimentation to practice nucleotide compound and polymers containing these compounds without such detailed and lengthy procedural guidance. In summary, such detailed and lengthy guidance is instantly set forth only for "SM" practice directed to ribose or deoxyribose and it is deemed undue experimentation to practice "SM" moieties other than ribose and deoxyribose given the limited instant disclosure. This rejection is reiterated and newly applied as necessitated by amendment due to newly added claims. The rejection has not been argued on its merits other than pointing to issued patents.

The rejection for lack of enablement is respectfully traversed.

Applicants respectfully maintain that the original specification amply provides an enabling disclosure for all of the subject matter now being claimed.

Reconsideration and withdrawal of the nonenablement rejection is respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 284-372 stand rejected for indefiniteness under 35 U.S.C. § 112, second paragraph. In the Office Action (pages 10-13), the Examiner stated:

> Claims 337-372 are vague and indefinite because duplicate and confusing step notations are present. For example, claim 337, lines 4 and 14 both cited step (l). Also, claim 337, third from the last line, confusingly cites step (b) without any corresponding step (a). Claim 348, last line of step (B), cites a (b) without a corresponding (a). Also, this (b) is the second (b) because there is a (b) in line 20. These rejections are necessitated by amendment.
>
> Claim 284, part (b), cites the detection of the presence of "oligo- or polynucleotides which have hybridized to said nucleic acid of interest" but is vague and indefinite when considered in view of part (a) of the claim. Said part (a) cites the practice of "hybridizing..." without any selectivity or specificity directed to preventing hybridization to nucleic acids that are not the "nucleic acid of interest". Thus, such "permitting" practice is reasonably interpreted as inclusive of all levels of stringency including conditions where hybridization is permitted to not only "nucleic acid of interest" but also to other nucleic acids that may be only 90% complementary, 70% complementary, or even only 20% complementary, etc. to the "oligo- or polynucleotide" cited in part (a). With this broad complementarity practice possible within the scope of part (a), what is meant by applicants' citation of the detecting practice of part (b)? Do applicants mean that selectivity or specificity is to be practiced at the detection step and not at the hybridization step? This suggests that the detecting step is not just a detecting step but is also inclusive of some selection practice. Such a selection practice is not given in step (b) as presently worded. It is noted that the commonly performed practice of a hybridization assay is to control the hybridization step, herein step (a) rather than step (b), so as to be selective as desired. Then the detection step is only directed to the detection of a signal which is then indicative of the presence of the "nucleic acid of interest" in the sample. This, however, is not how claim 284 is presently worded. This unclarity causes even more concern regarding claims such as 324 or 325 which are directed to genetic disorder detection. Additionally there is no mention of the "Sig" moiety in the detection practice of step (b) whereas it is the only "detectable" moiety that is cited in part (a). Do applicants intend that the detection practice of part (b) is inclusive of detection without use of the "Sig" moiety from part (a)? Alternatively, if detection of the "Sig" moiety of part (a) is intended to be the manner of detection of hybridization in part (b), why is part (b) silent regarding said "Sig"

moiety? Clarification is requested as to what applicants mean for the metes and bounds of parts (a) and (b) regarding how the presence of the "nucleic acid of interest" is indicated in the sample versus nucleic acids that are not of interest and what signal is determinative of said presence. Do applicants mean to include some selectivity in either of parts (a) or (b) and, if so, which part or parts? This unclarity is present in all of the instantly depending claims due to their direct or indirect dependence from any of the instant independent claims. This rejection is reiterated and newly applied as necessitated by amendment due to newly added claims.

All of the instant independent claims and those dependent therefrom directly or indirectly all are vague and indefinite because the metes and bounds of the positions on the base at which the Sig moiety is covalently attached is not commensurate with the various disclosures in the specification. See, for example, the directive on page 53, lines 1-4, which limits the modifications as to not interfering with the formation of a double-helix which is not recited in the claims. This rejection is reiterated and newly applied as necessitated by amendment due to newly added claims.

Claims 329-336 and 348-372 are vague and indefinite as to what is meant by "self-signalling", "self-indicating", or "self-detecting" because signals in assays must be received outside of the reaction moieties in order to record the reaction event. What, therefore, is meant by "self-..." which suggests the signal being turned in unto itself? Clarification is requested. This rejection is necessitated by amendment.

The indefiniteness rejection is respectfully traversed.

Applicants believe that the amendments to claims 284, 337 and 348 obviate many of the grounds for the indefiniteness rejection.

In view of the amendments to the claims, Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejection.

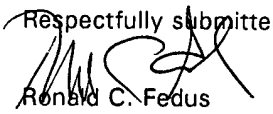
SUMMARY AND CONCLUSIONS

Claims 284-372 are presented for further examination on the merits. Claims 284, 337 and 348 have been amended. No other claims have been amended, canceled or added by this Amendment.

No fee is deemed necessary in connection with the filing of this amendment, other than the fee under 37 C.F.R. §1.17(r) for requesting the withdrawal of the finality of the January 6, 1998 Office Action and the three month extension request. If any other fee is deemed necessary, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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